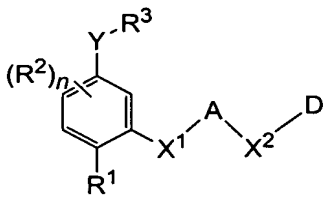
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claim 1 (Currently amended) A compound that has formula I:



I

or a pharmaceutically acceptable derivative thereof, wherein:

R^1 is halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or

S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in (-NR^6R^7) or (-NR^7R^8)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected

from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 2 (Original): The compound of claim 1, wherein R^1 is lower alkyl, lower cycloalkyl, alkenyl or alkynyl.

Claim 3 (Currently amended) The compound of claim 1 ~~or claim 2~~, wherein R^1 is methyl, halo, hydroxyl, lower alkyl, lower cycloalkyl, lower alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$ or $-NR^4R^5$.

Claim 4 (Currently amended) The compound of claims 1-~~3~~, wherein R^1 is methyl, halo, hydroxyl, lower alkyl, lower cycloalkyl, lower alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ or $-OR^4$.

Claim 5 (Currently amended) The compound of claims 1-~~4~~, wherein R^1 is methyl, hydroxyl, lower alkyl, lower cycloalkyl, lower alkynyl, trifluoromethyl, methoxy, trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ or $-OR^4$.

Claim 6 (Currently amended) The compound of claims 1-~~5~~, wherein R^1 is lower alkyl.

Claim 7 (Currently amended) The compound of claims 1-~~6~~, wherein R^1 is methyl.

Claim 8 (Currently amended) The compound of claims 1-~~7~~, wherein R^2 is alkyl or cycloalkyl.

Claim 9 (Currently amended) The compound of claims 1-~~8~~, wherein R^2 is alkyl.

Claim 10 (Currently amended) The compound of claims 1-~~9~~, wherein R^2 is hydrogen.

Claim 11 (Currently amended) The compound of claims 1-~~10~~, wherein R^3 is selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, heterocyclyl and heteroaryl.

Claim 12 (Currently amended) The compound of claims 1-~~10~~, wherein R^3 is selected from alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle.

Claim 13 (Currently amended) The compound of claims 1-~~12~~, wherein R^3 is cycloalkyl, cycloalkylalkyl, alkoxyalkyl or heteroaryl.

Claim 14 (Currently amended) The compound of claims ~~1-13~~, wherein R^3 is methyl, isopropyl, ethyl, cyclopropyl, cyclopropylmethyl, methoxymethyl, oxazolyl or thiazolyl.

Claim 15 (Currently amended) The compound of ~~calims 1-14~~ claim 1, wherein R^3 is cyclopropyl.

Claim 16 (Currently amended) The compound of claims ~~1-15~~, wherein Y is –C(=O)NH- or -SO_2NH-.

Claim 17 (Currently amended) The compound of claims ~~1-16~~, wherein Y is -C(=O)NH-.

Claim 18 (Currently amended) The compound of claims ~~1-17~~, wherein X^1 is a single bond or alkylene.

Claim 19 (Currently amended) The compound of claims ~~1-18~~, wherein X^1 is a single bond or -CH_2-.

Claim 20 (Currently amended) The compound of claims ~~1-19~~, wherein X^1 is a single bond.

Claim 21 (Currently amended) The compound of claims ~~1-20~~, wherein A is a bicyclic heterocyclic ring system, where each ring contains at least one N atom, and is optionally substituted with up to two R^{13}.

Claim 22 (Currently amended) The compound of claims ~~1-21~~, wherein A is a bicyclic heteroaryl ring system, where each ring contains at least one N atom, and is optionally substituted with up to two R^{13}.

Claim 23 (Currently amended) The compound of claims ~~1-22~~, wherein A is a bicyclic heteroaryl ring system, where each ring contains two N atoms, and is optionally substituted with up to two R^{13}.

Claim 24 (Currently amended) The compound of claims ~~1-23~~, wherein A is an imidazolopyrimidine, pyrrazolopyrimidine, imidazolopyrimidinone or pyrazolopyrimidinone group.

Claim 25 (Currently amended) The compound of claims ~~1-24~~, wherein A is a imidazolopyrimidine or a pyrazolopyrimidine group.

Claim 26 (Currently amended) The compound of claims ~~1-25~~, wherein X^2 is a single bond, alkylene or -NH-.

Claim 27 (Currently amended) The compound of claims ~~1-26~~, wherein X^2 is a single bond, -CH_2- or -NH-.

Claim 28 (Currently amended) The compound of claims ~~1-27~~, wherein X^2 is a single bond.

Claim 29 (Currently amended) The compound of claims 1-~~28~~, wherein D is heterocyclyl, cycloalkyl, heteroaryl or aryl, and is optionally substituted by one to four, in one embodiment one or two, $(CR^9R^{10})_wE$ groups.

Claim 30 (Currently amended) The compound of claims 1-~~29~~, wherein D is cyclohexyl, cyclopentyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl or phenyl, and is optionally substituted by one to four, in one embodiment one or two, $(CR^9R^{10})_wE$ groups.

Claim 31 (Currently amended) The compound of claims 1-~~30~~, wherein D is phenyl and is optionally substituted by one to four, in one embodiment one or two, $(CR^9R^{10})_wE$ groups.

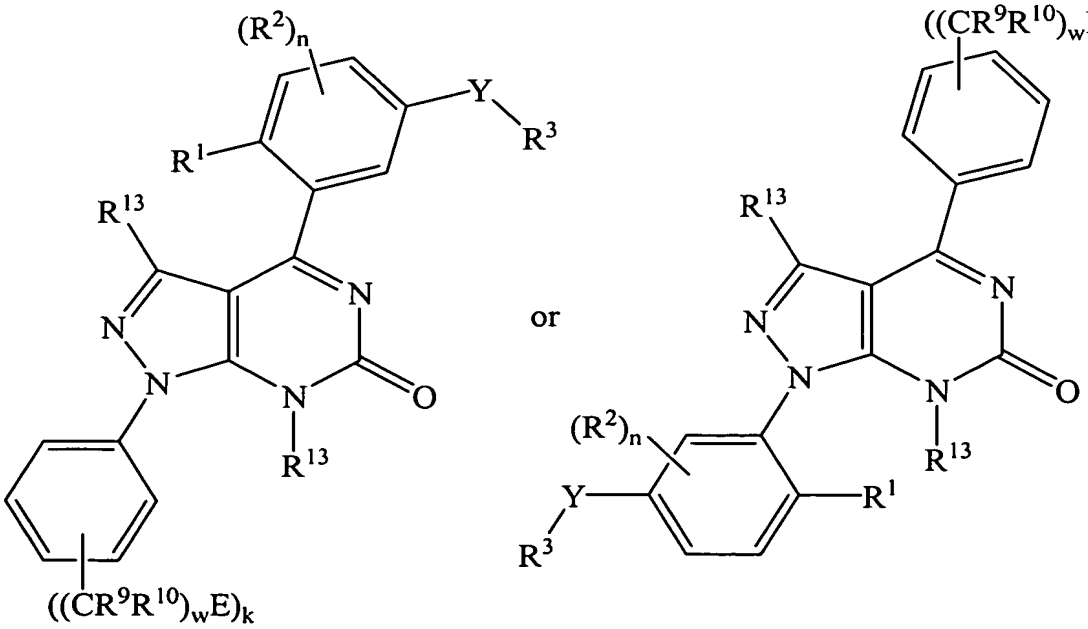
Claim 32 (Currently amended) The compound of claims 1-~~31~~, wherein R^{13} is alkyl, OH or NH_2.

Claim 33 (Currently amended) The compound of claims 1-~~32~~, wherein R^{13} is methyl, OH or NH_2.

Claim 34 (Currently amended) The compound of claims 1-~~33~~, wherein $(CR^9R^{10})_wE$ is alkyl, alkoxy, halo, -CH2-heterocyclyl, -CONH-cycloalkyl, alkylsulfonyl, alkylthio, alkylsulfonylamino, haloalkyl, aminocarbonyl, pseudohalo or heterocyclyl, or two $(CR^9R^{10})_wE$ groups, which substitute adjacent atoms on D, together form alkylenedioxy.

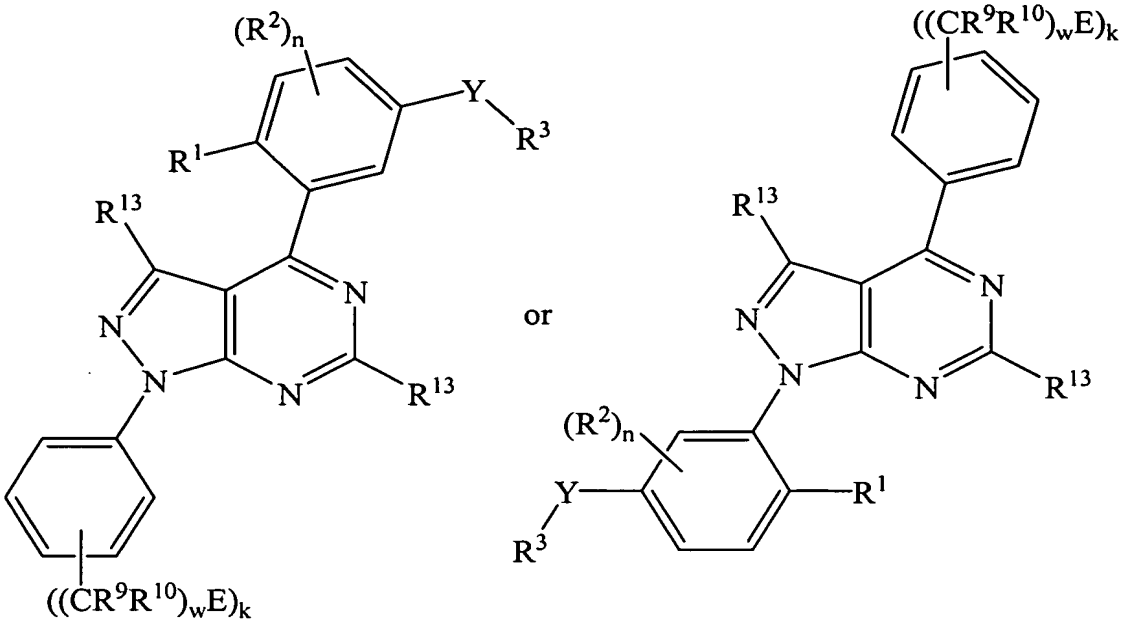
Claim 35 (Currently amended) The compound of claims 1-~~34~~, wherein $(CR^9R^{10})_wE$ is methoxy, methyl, 1,2,4-triazolyl, methylsulfonyl, ethoxy, 4-methyl-1-piperazinylmethyl, fluoro, chloro, cyclohexylaminocarbonyl, methanesulfonylamino, methylthio, 4-morpholinyl, trifluoromethyl, aminocarbonyl, iodo, cyano or cyclopropylaminocarbonyl, or two $(CR^9R^{10})_wE$ groups, which substitute adjacent atoms on D, together form methylenedioxy or ethylenedioxy.

Claim 36 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has ~~formulae~~ formula II:



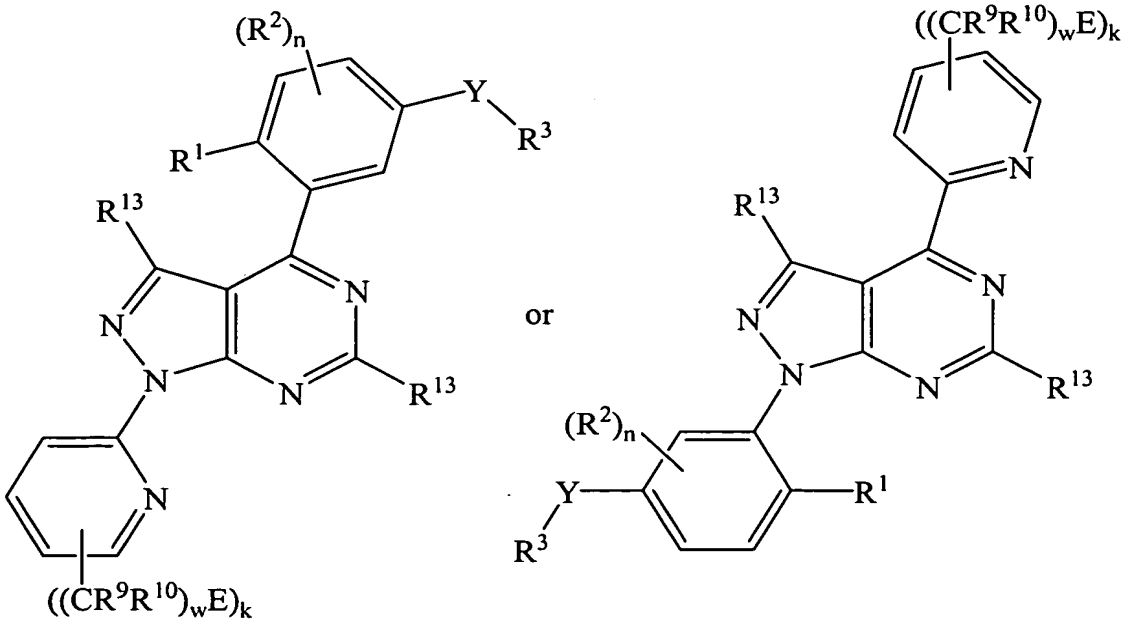
wherein k is an integer from 0 to 4.

Claim 37 (Currently amended) The compound of ~~any of claims 1-35~~ claim 1, wherein the compound has formula III:



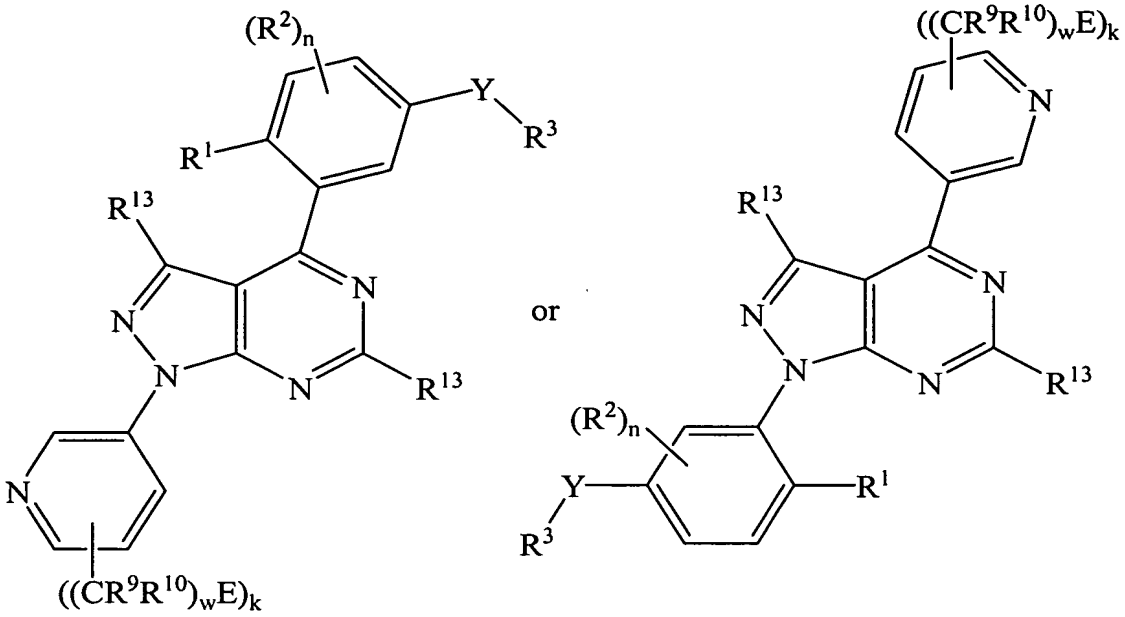
wherein k is an integer from 0 to 4.

Claim 38 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula IV:



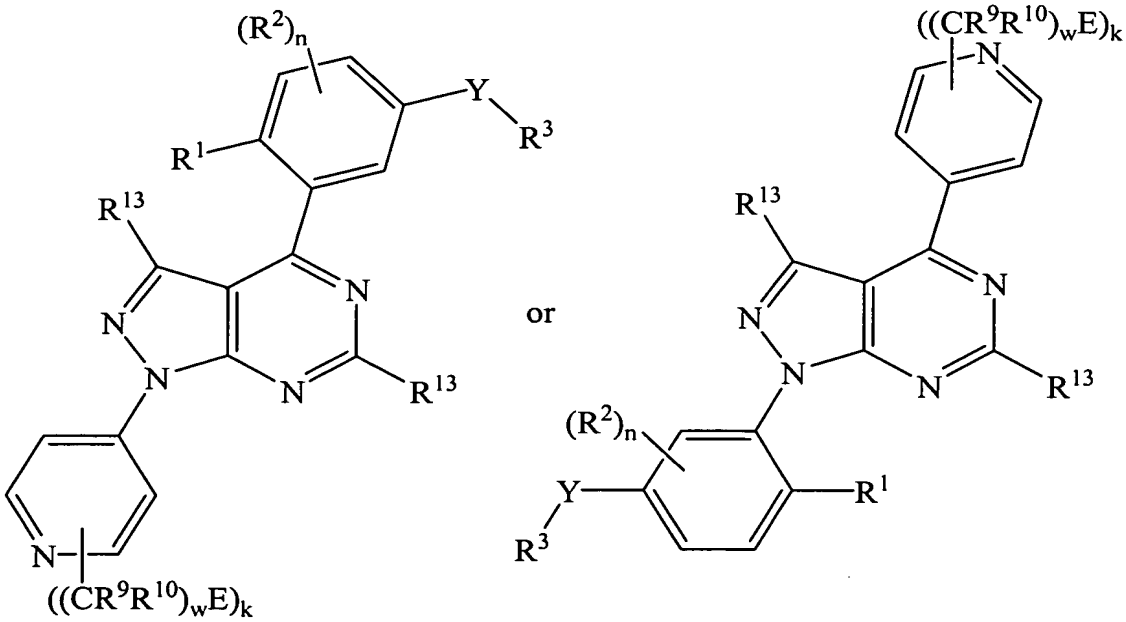
wherein k is an integer from 0 to 4.

Claim 39 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula V:



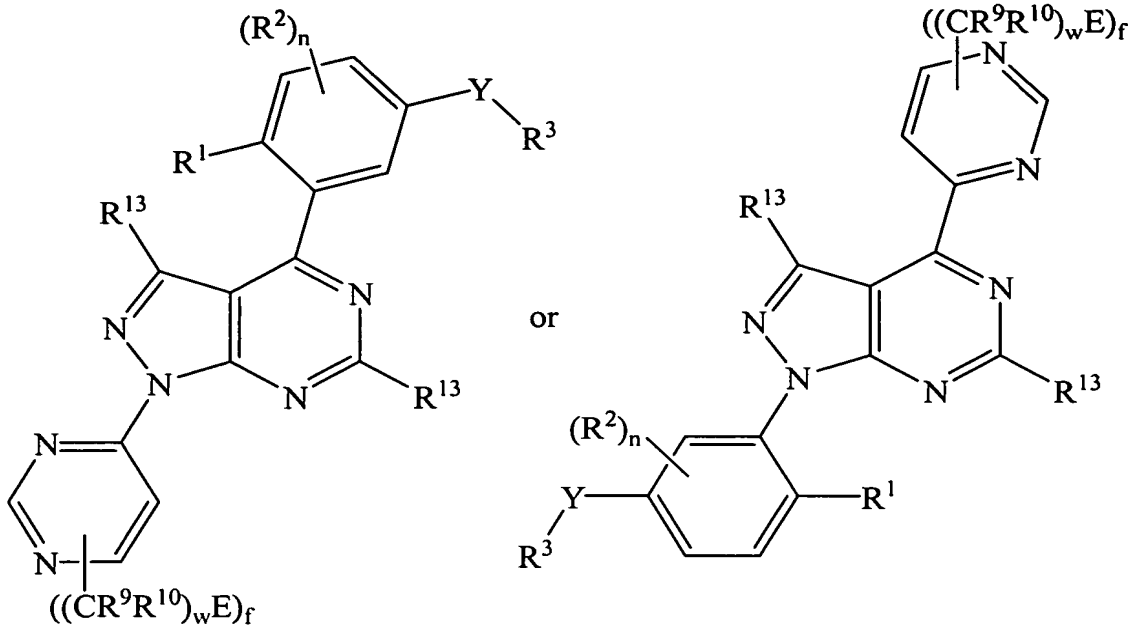
wherein k is an integer from 0 to 4.

Claim 40 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula VI:



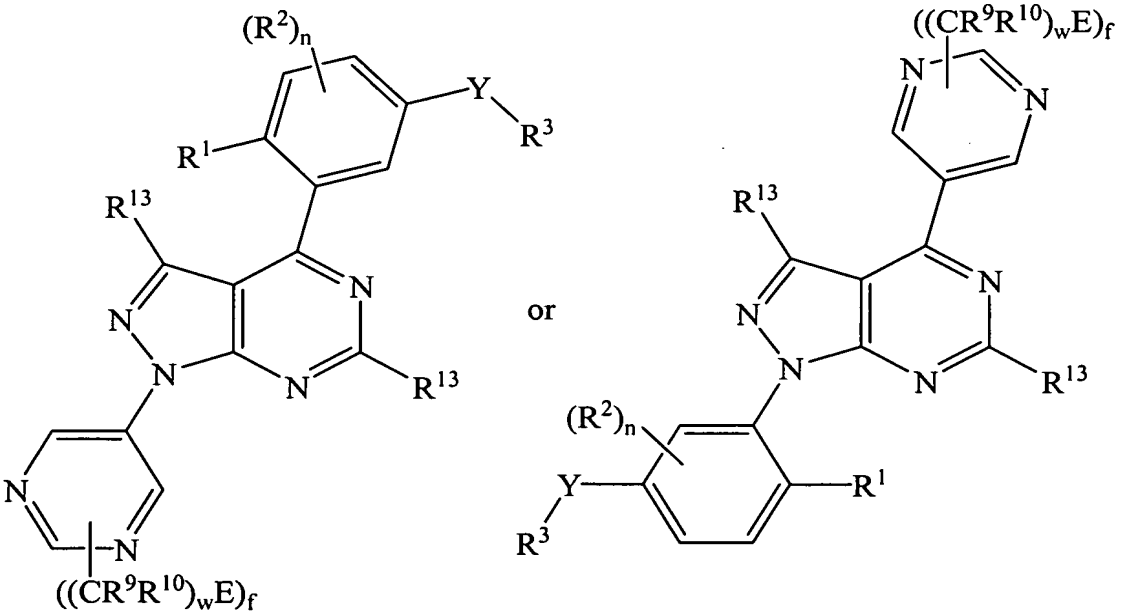
wherein k is an integer from 0 to 4.

Claim 41 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula VII:



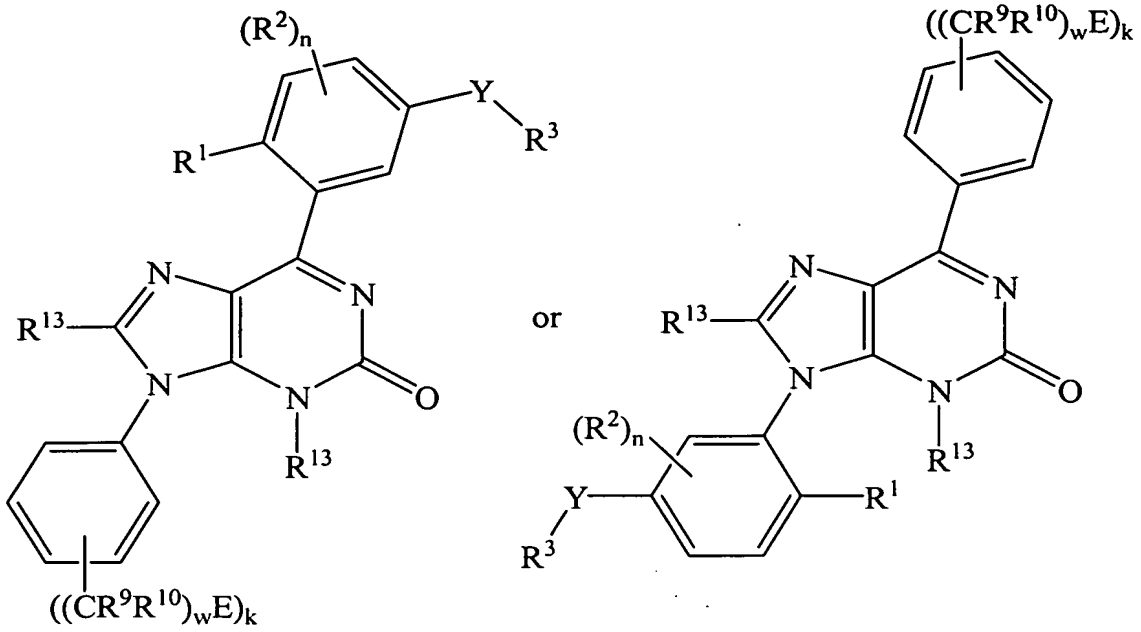
wherein f is an integer from 0 to 3.

Claim 42 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula VIII:



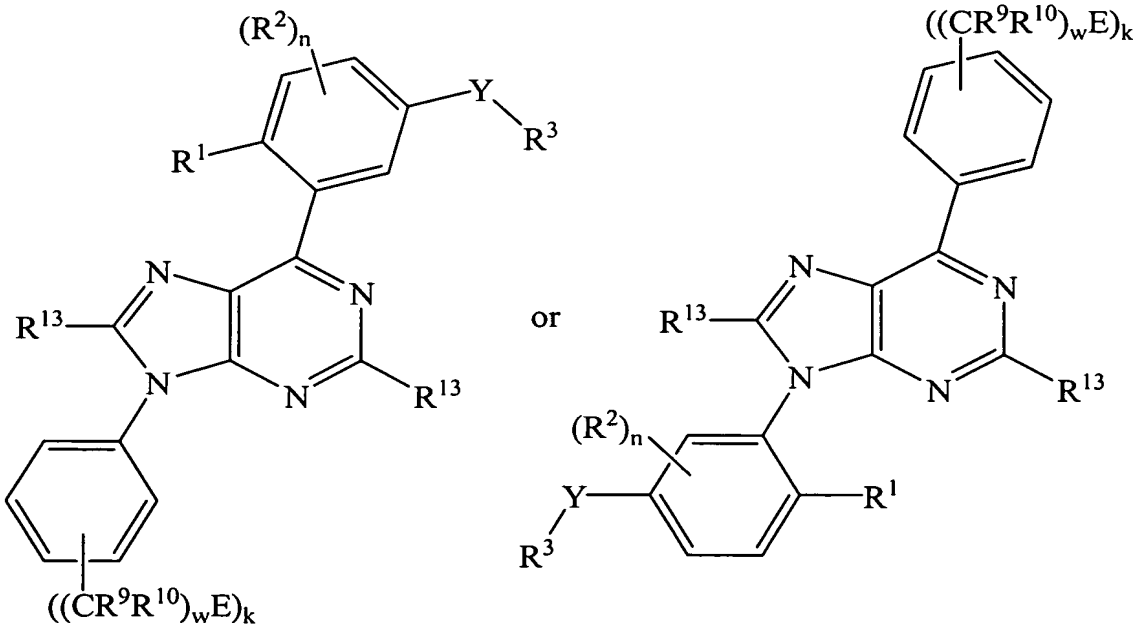
wherein f is an integer from 0 to 3.

Claim 43 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has ~~formulae~~ formula IX:



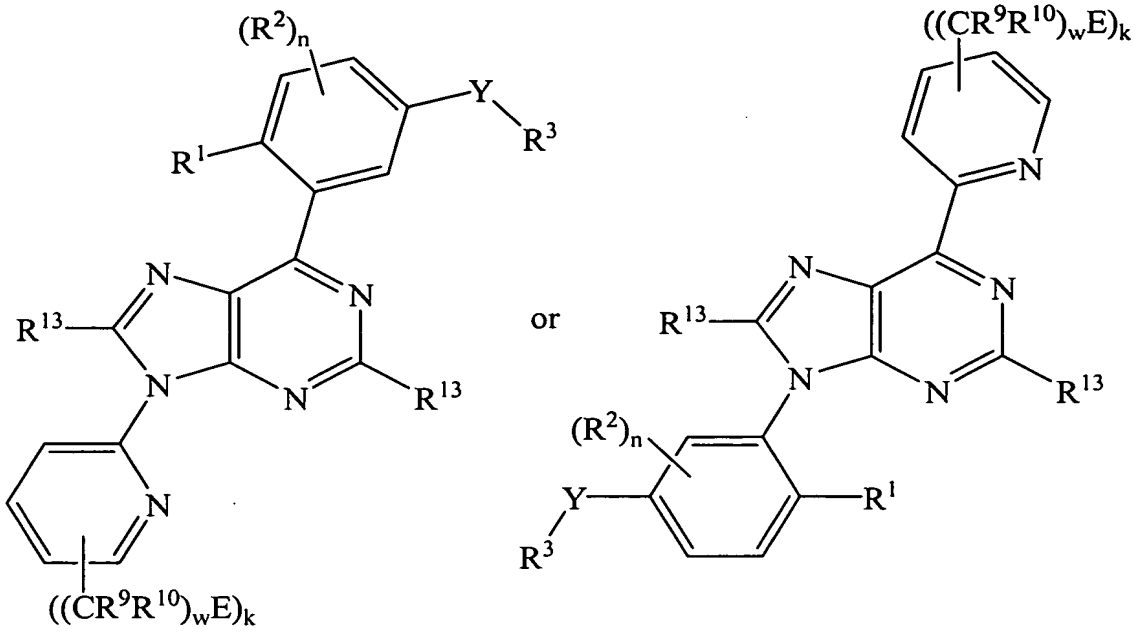
where k is an integer from 0 to 4.

Claim 44 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula X:



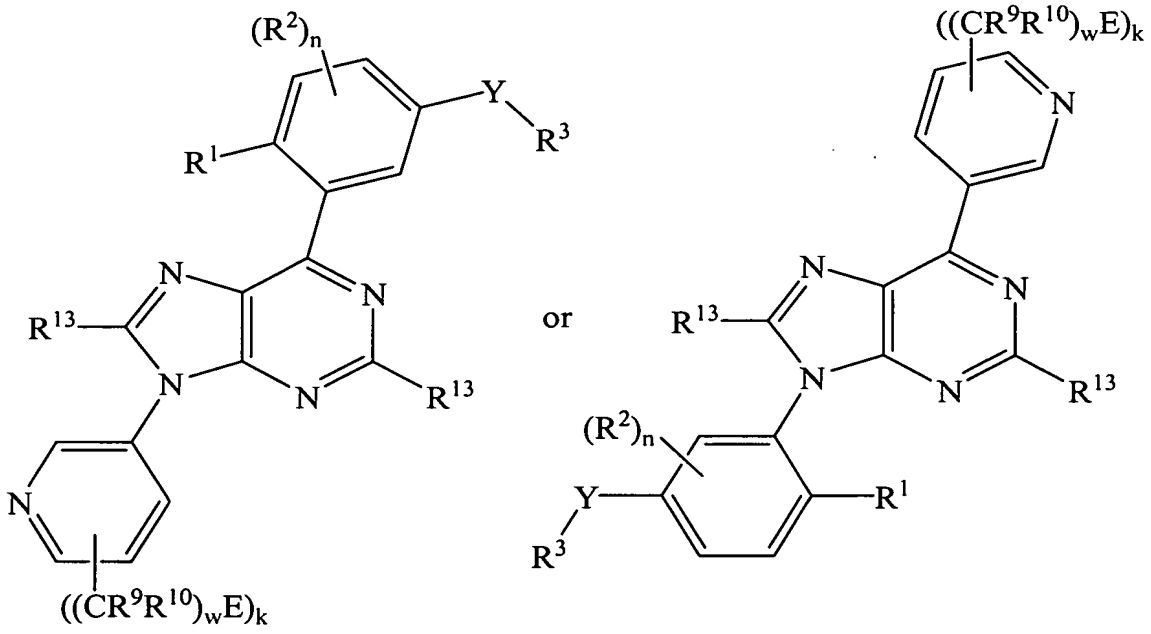
wherein k is an integer from 0 to 4.

Claim 45 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula XI:



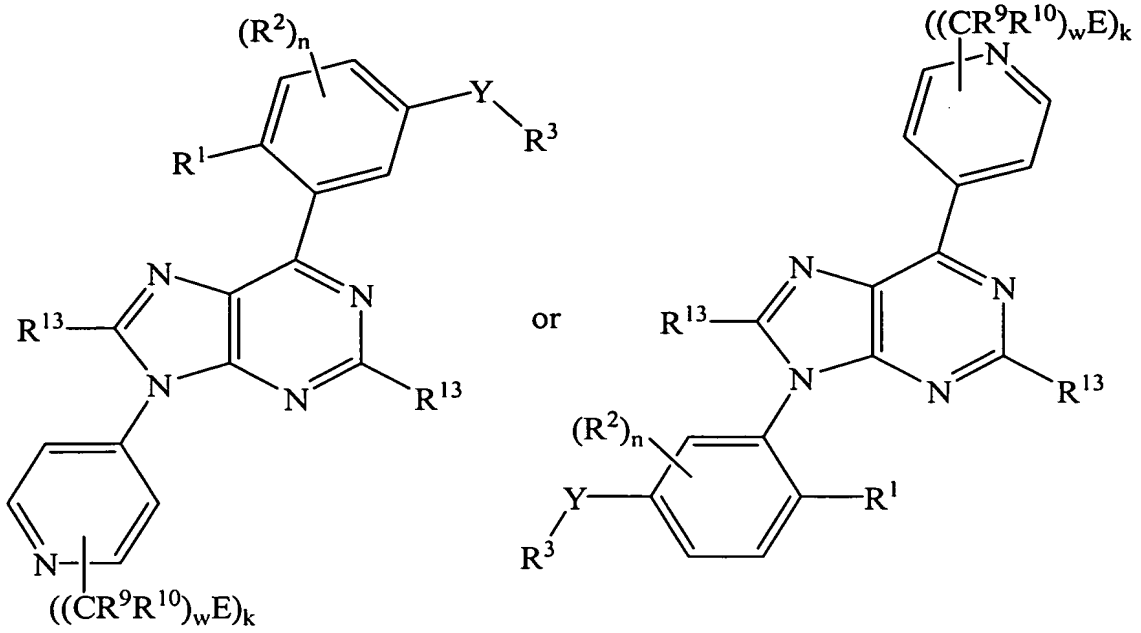
wherein k is an integer from 0 to 4.

Claim 46 (Currently amended) The compound of claim 1-~~35~~, wherein the compound has formula XII:



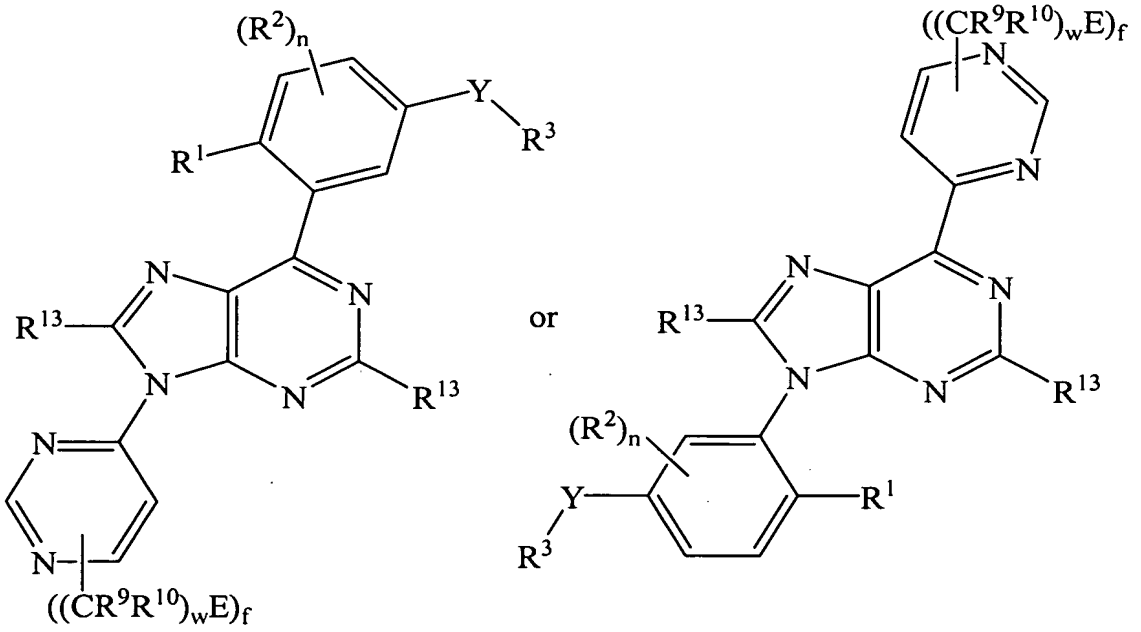
wherein k is an integer from 0 to 4.

Claim 47 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula XIII:



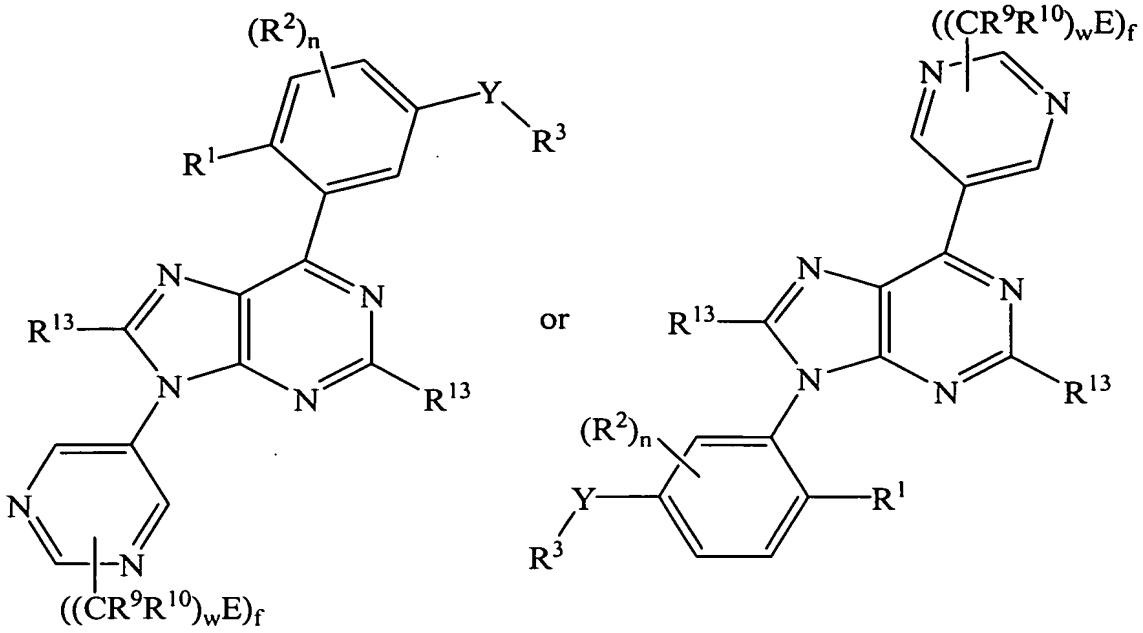
wherein k is an integer from 0 to 4.

Claim 48 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula XIV:



wherein f is an integer from 0 to 3.

Claim 49 (Currently amended) The compound of claims 1-~~35~~, wherein the compound has formula XV:



wherein f is an integer from 0 to 3.

Claim 50 (Currently amended) The compound of claims 1-~~49~~, wherein the compound is selected from those shown in the EXAMPLES.

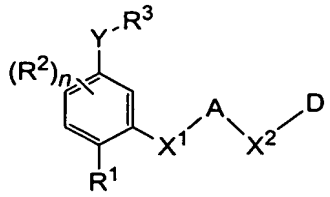
Claim 51 (Currently amended) A pharmaceutical composition, comprising a compound of ~~any of claims 1-50 and 95-103~~ claim 1 and a pharmaceutically acceptable carrier.

Claim 52 (Original) The pharmaceutical composition of claim 51 that is formulated for single dosage administration.

Claim 53 (Currently amended) A compound of ~~claims 1-50 and 95-103~~ claim 1 when use in the treatment of a p38 kinase mediated disease.

Claim 54 (Currently amended) Use of a compound of ~~claims 1-50 and 95-103~~ claim 1 in the preparation of a medicament for the treatment of a p38 kinase mediated disease.

Claim 55 (Currently amended) A method of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder that is modulated or otherwise affected by cytokine activity or in which cytokine activity is implicated, comprising administering to a patient in need thereof an effective amount of a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, $-C(=O)NH-$,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH-$, $-NHSO_2-$ or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7,

$SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 56 (Original) The method of claim 55, wherein the cytokine activity is modulated by p38 kinase.

Claim 57 (Currently amended) The method of claim~~s~~ 55 ~~or 56~~, wherein the p38 kinase is p38α, p38β, p38γ or p38δ.

Claim 58 (Currently amended) The method of ~~any of claims~~ claim 55~~-57~~, wherein the disease or disorder is selected from inflammatory disease, autoimmune disease, destructive bone disorder, proliferative disorder, angiogenic disorder, infectious disease, neurodegenerative disease and viral disease.

Claim 59 (Original) The method of claim 58, wherein the inflammatory disease is selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, and adult respiratory distress syndrome.

Claim 60 (Original) The method of claim 58, wherein the autoimmune disease is selected from glomeralonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis and graft vs. host disease.

Claim 61 (Original) The method of claim 58, wherein the destructive bone disorder is selected from osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Claim 62 (Original) The method of claim 58, wherein the proliferative disorder is selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

Claim 63 (Original) The method of claim 58, wherein the infectious disease is selected from sepsis, septic shock, and Shigellosis.

Claim 64 (Original) The method of claim 58, wherein the viral disease is selected from acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Claim 65 (Original) The method of claim 58, wherein the degenerative disease is selected from acute Alzheimer's disease, Parkinson's disease, cerebral ischemia, and other neurodegenerative diseases.

Claim 66 (Original) The method of claim 55, wherein the disease or disorder is modulated or otherwise affected by the activity of cytokine IL-1, TNF, IL-6 or IL-8.

Claim 67 (Original) The method of claim 66, wherein the disease or disorder is modulated or otherwise affected by the activity of cytokine IL-1.

Claim 68 (Currently amended) The method of claim 65 ~~or 66~~, wherein the cytokine IL-1 modulated disease or disorder is selected from rheumatoid arthritis, osteoarthritis, stroke, endotoxemia and/or toxic shock syndrome, inflammatory reaction induced by endotoxin, inflammatory bowel disease, tuberculosis, atherosclerosis, muscel degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, diabetes, pancreatic .beta.-cell disease and Alzheimer's disease.

Claim 69 (Currently amended) The method of claim 66 ~~or 67~~, wherein the cytokine TNFα modulated disease or disorder is selected from rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, AIDS, malignancy, keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis or pyresis.

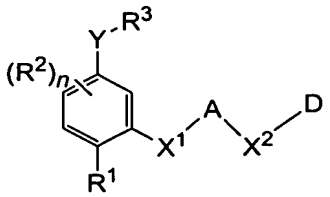
Claim 70 (Currently amended) The method of claim 66 ~~or 67~~, wherein the cytokine TNFα modulated disease or disorder is associated with a viral infection.

Claim 71 (Original) The method of claim 70, wherein the viral infection is selected from HIV, CMV, influenza and herpes.

Claim 72 (Original) The method of claim 70, wherein the viral infection is a veterinary virus infection caused by equine infectious anaemia virus, caprine arthritis virus, visna virus; maede virus, retrovirus infections.

Claim 73 (Currently amended) The method of claim 66 ~~or 67~~, wherein the cytokine IL-8 modulated disease or disorder is selected from psoriasis, inflammatory bowel disease, asthma, cardiac reperfusion injury, renal reperfusion injury, adult respiratory distress syndrome, thrombosis and glomerulonephritis.

Claim 74 (Currently amended) A method of reducing the expression of inducible pro-inflammatory proteins, comprising administering to a patient in need thereof an effective amount of a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, $-C(=O)NH-$,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH-$, $-NHSO_2-$ or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7,

$SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

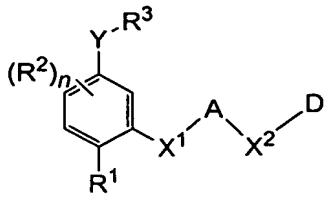
ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the. ~~The~~ substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 75 (Original) The method of claim 74, wherein the pro-inflammatory protein is prostaglandin endoperoxide synthase-2 (PGHS-2).

Claim 76 (Currently amended) A method of treating, preventing, or ameliorating one or more symptoms of diseases or disorders associated with inducible pro-inflammatory proteins, comprising administering to a subject in need thereof a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in (-NR^6R^7) or (-NR^7R^8)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

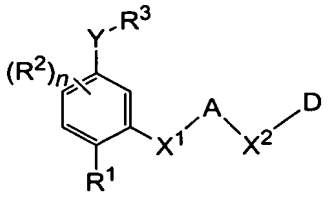
R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl,

carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the. ~~The~~ substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 77 (Original) The method of claim 76, wherein the disease or disorder is selected from edema, analgesia, fever, pain, neuromuscular pain, headache, pain caused by cancer, dental pain and arthritis pain.

Claim 78 (Currently amended) A method of inhibiting p38 kinase activity, comprising administering to a patient in need thereof an effective amount of a compound of formula I:



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or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -NH-C_{1-4}alkylene-, -N(C_{1-4}alkyl)-C_{1-4}alkylene-, -S(O)-, -SO_2-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio,

arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

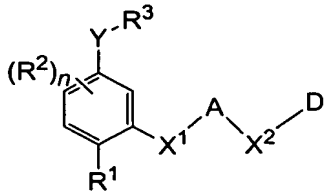
Claim 79 (Original) The method of claim 78, wherein the p38 kinase is selected from p38α kinase, p38β kinase, p38γ kinase and p38δ kinase.

Claim 80 (Currently amended) The method of claim 78 ~~or 79~~, wherein the p38 kinase is selected from p38α kinase and p38β kinase.

Claim 81 (Original) The method of claim 55, wherein the disease or disorder is selected from pancreatitis, asthma, allergies, adult respiratory distress syndrome, chronic obstructive pulmonary disease, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosis, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, graft vs. host disease, inflammatory reaction induced by endotoxin, tuberculosis, atherosclerosis, muscle degeneration, cachexia, psoriatic arthritis, Reiter's syndrome, gout, traumatic arthritis, rubella arthritis, acute synovitis, pancreatic β-cell disease; diseases characterized by massive neutrophil infiltration; rheumatoid spondylitis, gouty arthritis and other arthritic conditions, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoisosis, bone resorption disease, allograft rejections, fever and myalgias due to infection, cachexia secondary to infection, meloid formation, scar tissue formation, ulcerative colitis, pyresis, influenza, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, and Shigellosis; Alzheimer's disease,

Parkinson's disease, cerebral ischemias or neurodegenerative disease caused by traumatic injury; angiogenic disorders, solid tumors, ocular neovasculization, infantile haemangiomas; viral diseases, acute hepatitis infection, hepatitis A, hepatitis B, hepatitis C, HIV infection, CMV retinitis, AIDS, SARS, ARC, malignancy, herpes; stroke, myocardial ischemia, ischemia in stroke heart attacks, organ hyposia, vascular hyperplasia, cardiac and renal reperfusion injury, thrombosis, cardiac hypertrophy, thrombin induced platelet aggregation, endotoxemia and/or toxic shock syndrome, and conditions associated with prostaglandin endoperoxidase synthase-2.

Claim 82 (Currently amended) A method of inhibiting the activity of a kinase protein, comprising contacting the protein with a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl,

CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

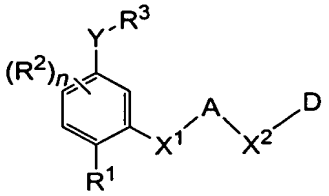
ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl,

CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 83 (Currently amended) A method of treating, preventing, or ameliorating one or more symptoms of a disease characterized by deregulation of the activity of a kinase protein, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -NH-C_{1-4}alkylene-, -N(C_{1-4}alkyl)-C_{1-4}alkylene-, -S(O)-, -SO_2-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in $(-NR^6R^7)$ or $(-NR^7R^8)$), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

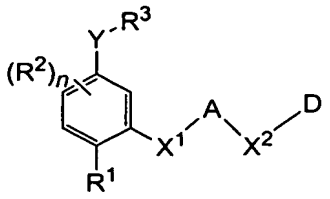
R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy,

alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 84 (Original) The method of claim 82, wherein the kinase protein is a tyrosine kinase protein.

Claim 85 (Original) The method of claim 82, wherein the kinase protein is FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, flt-1, IGF-1R, KDR, PDGFR, tie2 or VEGFR.

Claim 86 (Currently amended) A method of treating, preventing, or ameliorating one or more symptoms of disorders of the proliferation of blood vessels, fibrotic disorders, disorders of the proliferation of [["]]mesangial[["]] cells, metabolic disorders, allergies, asthma, thrombosis, diseases of the nervious system, retinopathy, psoriasis, rheumatoid arthritis, diabetes, muscle degeneration or cancer, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-$C_6alkyl)$, $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$,

$CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

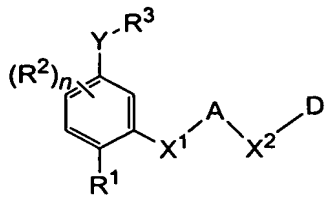
ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to

which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 87 (Currently amended) A method of treating, preventing, or ameliorating one or more symptoms of a disease associated with uncontrolled angiogenesis, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH,

C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

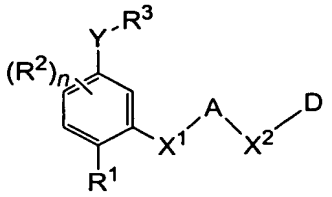
ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in (-NR^6R^7) or (-NR^7R^8)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono,

arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 88 (Currently amended) A method of treating, preventing, or ameliorating one or more symptoms of an oncologic disease, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)$-, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl,

CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

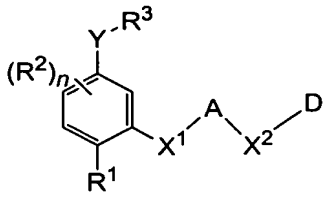
ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in ($-NR^6R^7$) or ($-NR^7R^8$)), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl,

CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 89 (Currently Amended) A method of treating, preventing, or ameliorating one or more symptoms of cancer, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, –C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH$-, $-NHSO_2$- or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2$-, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, -N(C_{1-4}alkyl)-, -NH-C_{1-4}alkylene-, N(C_{1-4}alkyl)-C_{1-4}alkylene-, -S(O)-, -SO_2-, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7, $SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in $(-NR^6R^7)$ or $(-NR^7R^8)$), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy,

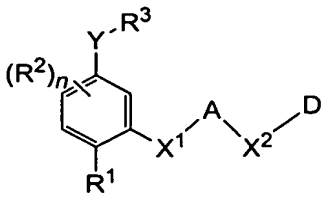
alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 90 (Original) The method of claim 89, wherein the disease is a solid tumor.

Claim 91 (Currently amended) The method of claim 89 ~~or 90~~, wherein the cancer is resistant to cytotoxic agents.

Claim 92 (Currently amended) The method of claim 89 ~~or 90~~, wherein the cancer is breast cancer, stomach cancer, cancer of the ovaries, cancer of the colon, lung cancer, brain cancer, cancer of the larynx, cancer of the lymphatic system, cancer of the genito-urinary tract including the bladder and the prostate, bone cancer and cancer of the pancreas.

Claim 93 (Currently Amended) A method of cancer chemotherapy, comprising administering a compound of formula I:



I

or pharmaceutically acceptable derivatives thereof, wherein:

R^1 is hydrogen, halo, alkyl, cycloalkyl, alkynyl, haloalkyl, alkoxy, haloalkoxy, pseudohalo, $-NR^4R^5$ or $-OR^4$;

R^2 at each occurrence is independently selected from alkyl, substituted alkyl, lower cycloalkyl, halo, trifluoromethyl, trifluoromethoxy, $-OR^4$, -CN, $-NR^4R^5$; -S(=O)alkyl, -S(=O)aryl, $-NHSO_2$-arylene-R^4, $-NHSO_2$alkyl, $-CO_2R^4$, $-CONH_2$, $-SO_3H$, -S(O)alkyl, -S(O)aryl, $-SO_2NHR^4$, and $-NHC(=O)NHR^4$;

n is 0, 1 or 2;

R^3 is selected from hydrogen, alkyl, $-OR^4$, substituted alkyl, cycloalkyl, $-CR^4$cycloalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

Y is a single bond, $-C(=O)NH-$,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH-$, $-NHSO_2-$ or -C(=O)-;

X^1 is a single bond, alkylene, -O-, -S-, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

A is a bicyclic heterocyclic ring system with at least one heteroatom in each ring, where the heteroatoms are each independently selected from N, O and S, and is optionally substituted with up to two R^{13};

X^2 is a single bond, alkylene, -O-, -S-, -NH-, $-N(C_{1-4}alkyl)-$, $-NH-C_{1-4}alkylene-$, $-N(C_{1-4}alkyl)-C_{1-4}alkylene-$, -S(O)-, $-SO_2-$, -C(O)-, -CO(O)- or -C(O)NH-;

D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), or D is C_{1-6}alkyl, and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups;

w is an integer from 0-4;

R^{10} is selected from H, C_1-C_4 alkylhydroxy, C_1-C_4alkylaryl and C_1-C_4alkylheteroaryl, wherein said aryl or heteroaryl group is unsubstituted or substituted with 1-3 groups independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, C_1-C_4alkoxy, C_1-C_4alkylcarbonyl, CN, NH_2, NR^6R^7, SR^6, $S(O)R^6$, SO_2R^6, SO_3R^6, SO_2NR^6, CO_2H, CO_2R^6, and $CONR^6R^7$;

E is selected from H, halogen, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6 alkynyl, haloalkyl, haloalkoxy, OH, OR^6, CN, CHO, CO_2R^6, $CONR^6R^7$, $OCOR_6$, $OC(=O)OR^6$, $OC(=O)NR^6R^7$, $OCH_2CO_2R^6$, $C(=O)R^6$, NH_2, NHR^6, NR^6R^7, $NR^7C(=O)R^6$, $NR^7C(=O)OR^6$, $NR^7C(=O)C(=O)OR^6$, $NR^7C(=O)C(=O)NR^6R^7$, $NR^7C(=O)C(=O)(C_1$-C_6alkyl), $NR^7C(=NCN)OR^6$, $NR^7C(=O)NR^6R^7$, $NR^7C(=NCN)NR^6R^7$, $NR^7C(=NR^6)NR^7R^8$, $NR^6SO_2NR^6R^7$, $NR^7SO_2R^6$, SR^6, $S(=O)R^6$, SO_2R^6, SO_3R^7,

$SO_2NR^6R^7$, NHOH, $NHOR^6$, $NR^6NR^7NR^8$, $N(COR^6)OH$, $N(CO_2R^6)OH$, $CONR^7(CR^9R^{10})_rR^6$, $CO(CR^9R^{10})_pO(CHR^9)_qCO_2R^6$, $CO(CR^9CR^{10})_rR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_pO(CHR^9)_qCO^2R_6$, $CO(CR^9CR^{10})_rOR^6$, $CO(CR^9R^{10})_pO(CR^9R^{10})_qR^6$, $CO(CR^6CR^{10})_rNR^6R^7$, $OC(O)O(CR^9R^{10})_mNR^6R^7$, $O(CO)_n(CR^9R^{10})R^6$, $O(CR^9R^{10})_mNR^6R^7$, $NR^7C(O)(CR^9R^{10})_rOR^6$, $NR^7C(=NC)(CR^9R^{10})_rR^6$, $NR^7CO(CR^9R^{10})_rNR^6R^7$, $NR^7(CR^9R^{10})_mOR^6$, $NR^7(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, NR^7, $NR^3(CR^9R^{10})_nSO_2(CR^9R^{10})_rCO_2R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $CONR^7(CR^9R^{10})_nSO_2(CR^9R^{10})_qR^6$, $SO_2NR^7(CR^9R^{10})_qR^6$, $SO_2NR^6(CR^9R^{10})_mOR^6$, C_2-C_6alkenyl, C_3-C_{10}cycloalkyl, C_3-C_{10}cycloalkylmethyl, aryl, heterocyclic optionally substituted with one or two alkyl groups, heteroaryl optionally substituted with one or two alkyl groups and alkylaryl, wherein said aryl groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from R^{12}, or two E groups, which substitute adjacent atoms on D, together form alkylenedioxy, thioalkyleneoxy or alkylenedithioxy;

m is an integer having a value from 2-6;

p is an integer having a value from 1-3;

q is an integer having a value from 0-3;

r is an integer having a value from 0-6;

R^{12} at each occurrence is independently selected from halo, NO_2, C_1-C_4alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, haloalkyl, haloalkoxy, OH, oxo, C_1-C_4alkoxy, OR^6, $O(CR^9R^{10})CO_2R^6$, $O(CR^9R^{10})_mNR^6R^7$, $O(CR^9R^{10})_pCN$, $O(CR^9R^{10})_rC(=O)NR^6R^7$, C_1-C_4alkylcarbonyl, CN, NH_2, NHR^6, NR^6R^7, $NR^7(CR^9R^{10})CO_2R^6$, NR^7OR^6, $NR^7(CR^9R^{10})_mOR^6$, $NR^7CH((CR^9R^{10})_pOR^6)_2$, $NR^7C((CR^9R^{10})_pOR^6)_3$, $NR^7C(=O)R^6$, $NR^7(CR^9R^{10})_mNR^6R^7$, $NR^7(CR^9R^{10})_qR^6$, SR^7, $S(O)R^7$, SO_2R^7, SO_2NR^6, SO_3R^7, CO_2H, CO_2R^6, and $CONR^6R^7$;

R^4 is hydrogen, lower alkyl and lower cycloalkyl;

R^5 is hydrogen, lower alkyl and lower cycloalkyl;

R^6, R^7 and R^8 are independently selected as follows:

i) R^6, R^7 and R^8 are independently selected from H, C_1-C_6alkyl, C_3-C_{10}cycloalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_3-C_7cycloalkyl(C_0-C_5alkyl)carbonyl, C_1-C_6alkoxy-carbonyl, aryl(C_0-C_5alkyl)carbonyl, aryl(C_1-C_5alkoxy)carbonyl, heterocyclic(C_0-C_5alkyl)carbonyl, heterocyclic(C_1-C_5alkoxy)carbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, C_0-C_4alkylaryl, C_0-C_4alkylheterocyclic, wherein said cycloalkyl, aryl, or heterocyclic groups are unsubstituted or substituted with 1 or 2 substituents each independently selected from the group consisting of C_1-C_4alkyl, hydroxyl, C_1-C_4alkoxy, F, Cl, Br, haloalkyl, NO_2 and CN; or,

ii) R^6 and R^7, or R^6 and R^8, or R^7 and R^8, when both substituents are on the same nitrogen atom (as in $(-NR^6R^7)$ or $(-NR^7R^8)$), can be taken together with the nitrogen atom to which they are attached to form a heterocycle selected from 1-aziridinyl, 1-azetidinyl, 1-piperidinyl, 1-morpholinyl, 1-pyrrolidinyl, thiamorpholinyl, thiazolidinyl, 1-piperazinyl, 1-imidazolyl, 3-azabicyclo(3,2,2)nonan-3yl, and 1-tetrazolyl, the said heterocycle being optionally substituted with 1-3 groups each independently selected from oxo, C_0-C_4alkylOH, C_0-C_4alkylOC_1-C_4alkyl, C_0-C_4alkyl$CONH_2$, C_0-C_4alkylCO_2C_0-C_4alkyl, C_1-C_4alkyl, C_1-C_4alkoxy, C_3-C_7cycloalkyl, C_0-C_6alkylcarbonyl, C_3-C_7cycloalkylcarbonyl, C_1-C_6alkoxycarbonyl, C_3-C_7cycloalkoxycarbonyl, -NHCOalkyl, aryl, heteroaryl, arylalkoxycarbonyl, heteroarylalkoxycarbonyl, C_1-C_6alkylsulfonyl, arylsulfonyl and heteroarylsulfonyl;

R^9 is hydrogen or C_1-C_4alkyl; and

R^{13} is hydrogen, alkyl, haloalkyl, aminocarbonyl, hydroxy, hydroxycarbonyl, alkoxycarbonyl, cycloalkylalkylaminocarbonyl, substituted alkyl, aryl, substituted aryl, heteroaryl, heterocyclyl, alkylthio, alkylaminocarbonyl or lower cycloalkyl; where the substituents on alkyl group are selected from one to four substituents selected from halo, hydroxy, alkoxy, oxo (=O), alkanoyl, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, aralkylamino, disubstituted amines in which the 2 amino substituents are selected from alkyl, aryl or aralkyl; alkanoylamino, aroylamino, aralkanoylamino, substituted alkanoylamino, substituted arylamino, substituted aralkanoylamino, thiol, alkylthio, arylthio, aralkylthio, alkylthiono, arylthiono, aralkylthiono, alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, sulfonamido, ~~e.g.~~ SO_2NH_2, substituted sulfonamido, nitro, cyano, carboxy, carbamyl, ~~e.g.~~ $CONH_2$, substituted carbamyl, ~~carbamyl e.g.~~ CONHalkyl, CONHaryl, CONHaralkyl or cases where there are two substituents on the nitrogen selected from alkyl, aryl or aralkyl; alkoxycarbonyl, aryl, substituted aryl, guanidino and substituted or unsubstituted heterocycles, such as indolyl, imidazolyl, furyl, thienyl, thiazolyl, pyrrolidyl, pyridyl, pyrimidyl and the like and the substituents on aryl group are selected from one to four substituents selected from alkyl, substituted alkyl, haloalkyl, halo, trifluoromethoxy, trifluoromethyl, hydroxy, hydroxyalkyl, aminoalkyl, alkoxy, alkanoyl, alkanoyloxy, amino, arylamino, aralkylamino, dialkylamino, alkanoylamino, thiol, alkylthio, ureido, nitro, cyano, cyanoalkyl, heterocyclyl, carboxy, carboxyalkyl, carbamyl, alkoxycarbonyl, aminocarbonyl, alkylthiono, arylthiono, arylsulfonylamine, sulfonic acid, alkysulfonyl, sulfonamido, aryloxy and $CONR^aR^b$, where R^a and R^b are selected from hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxycarbonylaminoalkyl and alkylamino; or R^a and R^b together with the nitrogen on which they are substituted, form a 3-6 membered heterocyclic or heteroaryl ring; the substituent may be further substituted by hydroxy, alkyl, alkoxy, aryl, substituted aryl, substituted alkyl or aralkyl.

Claim 94 (Currently amended) The method of ~~any of claims~~ claim 55-~~93~~, wherein R^1 is methyl, halo, hydroxyl, lower alkyl, lower cycloalkyl, lower alkynyl, trifluoromethyl, methoxy,

trifluoromethoxy, cyano, $-NH_2$, $-NR^4R^5$ or $-OR^4$; and Y is–C(=O)NH-,-NH(C=O)-, -NH(C=O)NH-, $-SO_2NH-$, $-NHSO_2-$ or -C(=O)-.

Claim 95 (Currently amended) The compound of ~~any of claims 1-50~~ claim 1, wherein when D is C_{1-6}alkyl, then X^2 is not a single bond or alkylene.

Claim 96 (Currently amended) The compound of ~~any of claims 1-50~~ claim 1, wherein D is a monocyclic or bicyclic aromatic or non-aromatic ring system optionally containing up to four heteroatoms selected from N, O, and S, and wherein a CH_2 adjacent to any of the said N, O or S heteroatoms is optionally substituted with oxo (=O), and wherein D is optionally substituted by one to four $(CR^9R^{10})_wE$ groups.

Claim 97 (Currently amended) The compound of ~~any of claims 1-50~~ claim 1, wherein D is C_{1-6}alkyl when X^2 is -NH-, $-N(C_{1-4}alkyl)-$, $-NH-C_{1-4}$alkylene-, $-N(C_{1-4}alkyl)-C_{1-4}$alkylene-.

Claim 98 (Currently amended) The compound of ~~claims 1-50 and 95-97~~ claim 1, wherein X^2 is a single bond, alkylene, $-N(C_{1-4}alkyl)-$ or -NH-.

Claim 99 (Currently amended) The compound of ~~claims 1-50 and 95-98~~ claim 1, wherein X^2 is a single bond, $-CH_2-$,-NH-, -N(Me)-, -N(Et)-, -N(n-Pr)-, -N(i-Pr)-, $-NNCH_2-$ or $-N(n-Pr)CH_2-$.

Claim 100 (Currently amended) The compound of ~~claims 1-50 and 95-99~~ claim 1, wherein D is azacinyl, diazepinyl, azepinyl, thiazolyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclopropyl, cyclobutyl, morpholinyl, piperazinyl, neopentyl, 1-methylisopentyl, 3-pentyl, 1,4-oxazepinyl, methyl, n-propyl, ethyl, 2-butyl, tert-butyl, tetrahydrofuranyl, tetrahydropyranyl, 7-azabicyclo[2.2.1]heptyl, cyclohexyl, cyclopentyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl or phenyl, and is optionally substituted by one to four, in one embodiment one or two, $(CR^9R^{10})_wE$ groups.

Claim 101 (Currently amended) The compound of ~~claims 1-50 and 95-100~~ claim 1, wherein D is azacinyl, diazepinyl, azepinyl, thiazolyl, cycloheptyl, bicyclo[2.2.1]heptyl, cyclopropyl, cyclobutyl, morpholinyl, piperazinyl, 1,4-oxazepinyl, tetrahydrofuranyl, tetrahydropyranyl, 7-azabicyclo[2.2.1]heptyl, cyclohexyl, cyclopentyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl or phenyl, and is optionally substituted by one to four, in one embodiment one or two, $(CR^9R^{10})_wE$ groups.

Claim 102 (Currently amended) The compound of ~~claims 1-50 and 95-101~~ claim 1, wherein $(CR^9R^{10})_wE$ is alkyl, alkoxy, halo, $-CH_2$-heterocyclyl, -CONH-cycloalkyl, alkylsulfonyl, alkylthio, alkylsulfonylamino, haloalkyl, aminocarbonyl, alkylcarbonyl, dialkylaminocarbonyl, alkylcarbonylamino, alkoxycarbonyl, hydroxyalkyl, alkoxyalkyl, heterocyclylalkyl, alkylcarbonyl-N(alkyl)-, cycloalkylaminocarbonyl, alkylaminocarbonyl, heteroaryl, dialkylaminoalkyl, pseudohalo or heterocyclyl, or two $(CR^9R^{10})_wE$ groups, which substitute adjacent atoms on D, together form alkylenedioxy.

Claim 103 (Currently amended) The compound of ~~claims 1-50 and 95-102~~ claim 1, wherein $(CR^9R^{10})_wE$ is methoxy, methyl, 1,2,4-triazolyl, methylsulfonyl, ethoxy, 4-methyl-1-piperazinylmethyl, fluoro, chloro, cyclohexylaminocarbonyl, methanesulfonylamino, methylthio, 4-morpholinyl, trifluoromethyl, aminocarbonyl, methoxycarbonyl, hydroxymethyl, ethoxycarbonyl, ethyl, methoxymethyl, methylcarbonylamino, dimethylaminocarbonyl, methylcarbonyl, dimethylaminomethyl, methylcarbonyl-N(Me)-, diethylaminomethyl, morpholinylmethyl, methylaminocarbonyl, 1,3,4-oxadiazolyl, cyclopropylaminocarbonyl, 5-methyl-1,3,4-oxadiazolyl, 5-ethyl-1,3,4-oxadiazolyl, iodo, cyano or cyclopropylaminocarbonyl, or two $(CR^9R^{10})_wE$ groups, which substitute adjacent atoms on D, together form methylenedioxy or ethylenedioxy.

Claim 104 (Cancelled)